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tDCS increases anxiety reactivity to intentional worry

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Abstract

While considerable experimental research has examined the impact of transcranial direct current stimulation (tDCS) on a range of cognitive processes associated with emotional pathology, the impact of tDCS on worry has been comparatively neglected. Given that anxiety pathology is characterised by motivated engagement in worry, and that frontal tDCS has the capacity to enhance goal-oriented cognition, it is important to examine whether tDCS would increase or ameliorate the cognitive and emotional effects of worry. In the current study we examined how tDCS influenced the anxiety response to worry, and the frequency of negative intrusive thoughts. We additionally examined whether stimulation delivered in isolation, or in combination with a mindful-focus task would augment the effects of tDCS. Ninety-seven (75 female) healthy participants received either active or sham anodal tDCS to the left dorsolateral prefrontal cortex, delivered either in isolation or concurrently with a mindful task (four conditions). The frequency of negative thought intrusions was assessed before and after a period of instructed worry, and state anxiety was assessed across the study. Active tDCS was associated with significantly greater elevation in anxiety in response to the worry induction. No effects were observed on the frequency of negative thought intrusions, and the combined delivery of tDCS with the concurrent mindful task did not alter the pattern of observed effects. While inviting replication in a high anxious sample, the present results highlight the possibility that tDCS may interact with motivated engagement in negative patterns of cognition, such as worry, to produce greater emotional reactivity.

Key words: Neurostimulation; tDCS; transcranial direct current stimulation; worry; anxiety

Introduction

Transcranial direct current stimulation (tDCS) is one of a number of emerging neuromodulatory interventions showing promise as a potential treatment for anxiety and mood disorders (Brunoni et al., 2016; Sagliano et al., 2019). While the vast majority of research examining therapeutic benefits of tDCS on emotional dysfunction has focused on depression (Brunoni et al., 2016), a small but growing number of studies have examined potential clinical benefits in anxiety disorders. While predominantly at the case study/series stage, this research suggests potentially promising effects of tDCS in the treatment of a number of anxiety disorders including generalised anxiety disorder (GAD) using excitatory stimulation of left prefrontal or inhibitory stimulation of right prefrontal areas (Sagliano et al., 2019; Vicario et al., 2019). Support for potential clinical benefits of tDCS in anxious populations has also come from experimental research showing positive effects of left dorsolateral prefrontal cortex stimulation (DLPFC) on neural, cognitive, and emotional processes relevant to anxiety (e.g. Baumert et al., 2019; Heeren et al., 2017; Ironside et al., 2019; Ironside et al., 2016). However, of particular relevance to the potential clinical applications of tDCS for anxiety disorders (and in particular GAD), we are aware of no experimental research that has sought to determine the effects of tDCS on a fundamental cognitive process operating in anxiety: worry.

A unique feature of worry in disorders such as GAD is that individuals frequently report positive beliefs regarding its benefits in planning for and avoiding potential future misfortunes (Borkovec et al., 1999). Such motivated engagement in worry, carries potential implications for the implementation of tDCS as an intervention in anxiety disorders such as GAD. This becomes particularly apparent when considering research showing that tDCS has the ability to enhance goal-oriented cognition.

Converging research indicates that tDCS can enhance specific patterns of cognition in line with an individual's active information processing goals. For example, Andrews et al. (2011) and Martin et al. (2013) demonstrated that left DLPFC tDCS (contralateral supraorbital and extracephalic cathode respectively) delivered with concurrent cognitive training results in significantly improved working memory performance compared with tDCS or cognitive training alone. Anodal tDCS to the left, but not the right DLPFC (contralateral supraorbital cathode) has also been shown to facilitate goal-directed cognition in the form of facilitated attentional disengagement from emotional content (Sanchez-Lopez et al., 2018). Findings have also revealed tDCS can enhance the ability to emotionally regulate in line with an individual's current goals. Feeser et al. (2014) demonstrated that individuals receiving tDCS to the right DLPFC (contralateral supraorbital cathode) were better able to both increase and decrease emotional reactivity to negative content relative to sham stimulation. Marques et al. (2018) also showed evidence for tDCS enhancement of emotional regulation, though only with left ventrolateral PFC (VLPFC) stimulation (contralateral cathode). While the stimulation locations vary considerably across studies these findings underscore the possibility that the emotional effects of tDCS may depend in part on the cognitive goals of the individual, with increases or decreases in emotional reactivity occurring in line with individuals' current active intent.

Considering the role of active cognitive goals, it is possible that tDCS could potentially *increase* the cognitive and emotional effects of worry if engagement in worry was an individual's explicit goal. The first key aim of the current study therefore was to determine the acute effect of tDCS on worry in terms cognitive (negative intrusive thoughts) and emotional (elevated anxiety) consequences. To achieve this we implemented a frequently used worry induction paradigm (Hayes, Hirsch, Krebs, et al., 2010; Ruscio & Borkovec, 2004).

This procedure involves a period of instructed worry, preceded and followed by a 5-min breathing focus period, during which the frequency of negative intrusive cognitions is assessed. The impact on anxiety was assessed through measures of anxious mood delivered before and after each stage of the worry induction task.

While considerable heterogeneity exists in neural areas targeted for stimulation among studies evaluating the cognitive and emotional effects of tDCS, perhaps one of the most consistently selected regions has been the left DLPFC. Neural models directly implicate left DLPFC activity in the regulation of anxiety (Bishop, 2007), with findings showing that left DLPFC tDCS can attenuate emotional reactivity to negative content (Peña-Gómez et al., 2011), facilitate attention control in line with goal-directed cognition (Andrews et al., 2011; Martin et al., 2013), reduce attentional vigilance for threat (Heeren et al., 2017; Ironside et al., 2016), and down-regulate amygdala response to threatening emotional content in high anxious individuals (Ironside et al., 2019). Thus, due to its apparent role in regulatory control of anxiety and emotional attention, the left DLPFC was deemed an appropriate target for stimulation in the current study.

We discern two alternative hypothesis regarding the potential effects of anodal tDCS to the left DLPFC on worry. If tDCS has a general anxiolytic effect, it follows that those receiving active tDCS would evidence less elevations in anxiety and fewer subsequent negative intrusive cognitions following a discrete period of instructed worry compared to those in the sham condition. Alternatively, if tDCS increases engagement in goal-oriented cognition, then we would anticipate greater emotional reactivity to the period of worry induction reflecting more intense worry-engagement. This hypothesis also predicts a larger decrease in anxiety and less perseveration of worry for those receiving active tDCS during the subsequent breathing focus period when cognitive goals shift to non-worry focus.

The second key aim of the current study was to assess whether an online task designed to increase attentional focus and discourage engagement with negative intrusive cognitions would augment the cognitive and emotional effects of tDCS on worry. While a number of candidate cognitive tasks could potentially be employed in conjunction with tDCS (e.g. working memory training, cognitive control training, cognitive bias modification) this study specifically considered the potential effects of combining tDCS with mindful meditation. Not only is mindfulness easily combined with tDCS but has been shown to be capable of ameliorating the cognitive and emotional effects of worry (Hofmann et al., 2010). Mindful meditation is also understood to exert effects on emotion via functional reorganisation of similar frontal-limbic connectivity commonly targeted by tDCS (Marchand, 2014) with mindfulness facilitating down-regulation of emotional responses via heightened prefrontal control of the amygdala (Chiesa et al., 2013). Similarly, during mindful meditation, increased DLPFC activity is specifically associated with the recruitment of executive attentional resources to disengage from distractions and sustain attention on the meditation object (Hasenkamp et al., 2012). As such, active and sham tDCS delivery conditions were combined with two alternative mindfulness conditions consisting of either a mindful-focus (body scan) task during tDCS delivery, or a mind-wandering condition that did not seek to encourage attentional focus. If mindful-focusing does interact with tDCS to enhance attentional focus and disengagement from negative intrusive cognitions, then those receiving tDCS combined with the mindful-focus task would show attenuated emotional reactions to the worry induction, fewer subsequent intrusive cognitions, and greater emotional recovery (anxiety reduction) following the worry induction task relative to those receiving tDCS combined with the mind-wandering task.

Methods and Materials

Participants

Ninety-seven individuals (75 female, 22 male) were recruited through Curtin University's School of Psychology. tDCS requirements precluded participation for anyone with a history of psychiatric or neurological disease, unstable medical condition, frequent migraines, current psychoactive medication, any active skin condition, faintness, or any metal implants, devices or hearing aid. Participants were made aware of this prior to registering for the study and again upon arrival. This research was conducted in accordance with the principles expressed in the Helsinki Declaration, as revised 1989. All procedures were approved by Curtin University's Human Research Ethics Committee.

Questionnaire measures

General emotional distress was assessed with the 21 item version of the Depression, Anxiety, and Stress scale (DASS; Lovibond & Lovibond, 1995) at baseline. Possible scores on each subscale range from 0-21. The internal consistency of the depression ($\alpha = .90$) anxiety ($\alpha = .81$) and stress ($\alpha = .84$) subscales was consistently high in the current study.

Anxious mood was assessed with an adapted version of the six-item short-form of the state version of the State Trait Anxiety Inventory (STAI-S; Marteau & Bekker, 1992). This was delivered at six time-points; see Figure 1. Participants responded to each item (e.g. "I feel relaxed", "I feel anxious") by clicking on a 100mm line displayed on screen with the anchors 'not at all' to 'extremely', with each response scaled from 0 to 100. Positive items were reverse coded, and all items were averaged to yield a state anxiety score out of 100 for each time point, with higher scores representing higher state anxiety.

Transcranial Direct Current Stimulation

tDCS was applied using a pair of saline-soaked sponge electrodes (30 cm²) and delivered via battery-driven, current-controlled stimulator (Chattanooga Group, Hixson, United States). Anodal stimulation targeted the left DLPFC, with the anode placed over F3 using the International 10-20 system. The cathode was placed on the left superior trapezius muscle. Consistent with a number of prior studies (Chen et al., 2017; Clarke et al., 2014; Martin et al., 2013), this extracephalic reference location was chosen to avoid potential confounding effects from inhibitory stimulation of other cortical sites. Current was set at 2.0mA for participants in the active-tDCS condition (current density = 0.07/cm²) and was applied for 20 min, which included 30s ramp up/down time. For the sham condition, current was set at 1.0mA and ran for one minute before being switched off without the participant's knowledge (30s ramp-down). The experimenter was aware of participant's tDCS condition allocation.

Mindful-focus/mind-wandering tasks

While receiving tDCS, participants in the mindful-focus condition engaged in a 14 minute guided body-scan meditation recorded for the purposes of the study. Body scan represents a common mindfulness task that does not rely on the generation of visual imagery (which can be a source of individual difference), and would not overlap with the breathing-focus task component of the intrusive thought assessment (as would be the case with breath-awareness mindfulness task). The audio instructed them to progressively attend to sensations arising in various parts of the body, and to gently return their attention to their body whenever they noticed that their mind had wandered. The mind-wandering control condition was employed as a comparison condition to assess the relative effects of mindfulness (with and without tDCS) in contrast to the patterns of cognition that

participants spontaneously engaged in without instruction. Those in the mind-wandering condition were instructed to sit quietly for an equivalent duration while receiving tDCS, and allow their mind to wander.

Filler task

To facilitate the extinction of any potential between-group differences in state anxiety elicited by the experimental conditions, participants completed a five-minute filler task (arrow identification task) following the completion of tDCS and mindful/mind-wandering tasks.

Worry induction and intrusive thought assessment

We adopted an online assessment of intrusive thoughts successfully used in a number of previous studies (Hayes, Hirsch, Krebs, et al., 2010; Hirsch et al., 2011). This task examines the frequency of intrusive thoughts during two five-minute breathing-focus periods delivered immediately before and after a five-minute worry induction. During the intrusive thought assessment, participants are instructed to focus on their breathing, and redirect their focus back to their breath whenever they noticed that their mind has wandered. During this 5-minute period, eleven tones sounded separated by 20-30 seconds (random within this window). The tone prompted participants to indicate whether they were focused on their breathing or on something else. If they indicated that they had been focused on something else, the participant was prompted to indicate whether the content of this thought was positive, neutral, or negative, and provide a brief (2-3 word description) of the content. They then returned to focus on their breathing.

Following the initial assessment of negative thought intrusions, participants received the worry induction procedure. For this, the experimenter assisted participants to identify a suitable topic of worry that they had thought about repeatedly over the last week (being

future-oriented and negative/threatening in nature). Once identified, the participant was instructed to actively worry about this for five minutes. Following the worry induction, the participant completed the post-worry intrusive thought assessment, which was identical to the first. The intrusive thought assessments was delivered on computer using Inquisit software (Inquisit 4.0.8, 2015). The key dependent measure from this task was the frequency of negative intrusive thoughts during the pre and post worry assessments which produced a possible score from 0-11.



Figure 1. Order and timing of experimental procedures. Participants initially completed baseline questionnaire (BQ) measures before electrode attachment and initiation of tDCS/sham stimulation. Five minutes of stimulation/sham was delivered before the mindfulness/mind wandering component began. In addition to completion at baseline, state anxiety (SA) was assessed post-tDCS, pre intrusion-assessment 1, pre worry-induction, post worry-induction, and post intrusion-assessment 2.

Data Analysis

Data preparation

Two participants recorded a high number of missing responses from multiple task components and were excluded from analyses. Participants with responses falling further than 3 SD from the group mean were considered outliers. Intrusions data of two participants and STAI-S scores of two participants met this exclusion criterion. These participants were excluded from each corresponding analysis¹.

¹ When analyses are run with the inclusion of all participants this did not change the direction or the significance of any effects.

Baseline group characteristics

Age, gender, STAI-S and DASS scores were compared across the four experimental conditions using a one-way ANOVA for continuous data, and chi-square tests for categorical data.

The effect of tDCS and mindful-focus on thought intrusions

To examine the effect of experimental conditions on the negative intrusive thoughts, a $2 \times 2 \times 2$ mixed model ANOVA was conducted with the between-subjects factors of tDCS condition (active-tDCS vs. sham-tDCS) and mindfulness condition (mindful-focus vs. mind-wandering), and the within-subjects factors of assessment point (pre- vs. post-worry induction) with the number of negative intrusive thoughts as the dependent variable.

The effect of tDCS and mindful-focus on state anxiety

To examine the effect of each experimental condition on state anxiety across the study, a $2 \times 2 \times 5$ mixed model ANOVA was conducted with the between-subjects factors of tDCS condition (active-tDCS vs. sham-tDCS) and mindfulness condition (mindful-focus vs. mind-wandering), and the repeated-measures factor of assessment point (five assessment points; see Figure 1), and STAI-S scores as the dependent measure.

Results

Baseline group characteristics

Groups did not differ in gender ratio, $\chi^2(3)=.437, p=.933$, age, $F(3, 94)=1.20, p=.31$, STAI-6, $F(3, 94)=0.80, p=.97$, or any DASS subscales, all $F<.77$, all $p>.51$. Descriptive data across experimental groups are provided in Table 1.

Table 1.

Descriptive statistics across experimental groups with gender ratio and means for age and emotional assessment measures at baseline. Standard deviations given in parentheses.

	Active-tDCS				Sham-tDCS			
	Mindful-focus		Mind-wandering		Mindful-focus		Mind-wandering	
Gender F/M	19/6		19/6		17/6		18/4	
Age	21.72	(4.09)	22.64	(5.89)	23.74	(9.97)	20.36	(2.08)
DASS-Depression	3.88	(3.43)	5.56	(4.72)	4.65	(5.36)	4.00	(3.49)
DASS-Anxiety	3.88	(4.01)	4.36	(3.30)	3.43	(3.46)	3.59	(3.45)
DASS-Stress	6.68	(5.06)	7.16	(3.64)	7.26	(4.50)	6.72	(3.39)
STAI-S	39.56	(18.01)	40.98	(19.31)	39.16	(19.51)	38.36	(18.50)

DASS = Depression Anxiety and Stress Scale; STAI-S = Short form of the state anxiety inventory.

The effect of tDCS and mindful-focus on thought intrusions

Descriptive data for thought intrusions are reported in Table 2. The only significant effect to emerge was a main effect of assessment point, $F(1,88) = 17.77$, $p < .001$, $\eta_p^2 = 0.168$, showing that participants on average experienced more frequent negative thought intrusions in the post-worry assessment period ($M = 1.22$, $SD = 1.38$) as compared to the pre-worry assessment period ($M = 0.65$, $SD = 0.84$). No other significant main effects or interactions were observed (all $F < 1.93$, all $p > .169$).

Table 2

Descriptive data showing the mean frequency of negative thought intrusions reported by participants during each of the assessment points – pre and post worry induction. Standard deviations given in parentheses.

	Active-tDCS				Sham-tDCS			
	Mindful-focus		Mind-wandering		Mindful-focus		Mind-wandering	
Pre worry-induction	0.83	(0.92)	0.56	(0.71)	0.62	(0.98)	0.59	(0.78)
Post worry-induction	1.33	(1.52)	1.52	(1.48)	1.27	(1.44)	1.21	(1.33)

The effect of tDCS and mindful-focus on state anxiety

A main effect of Assessment point, $F(4, 89)=67.67$, $p<.001$, $\eta_p^2=0.432$ showed that state anxiety was significantly higher post worry-induction than at any other time point (all $t>8.57$, all $p<.001$). This main effect was subsumed within a tDCS condition by assessment point interaction, $F(4, 89)=4.39$, $p=.002$, $\eta_p^2=0.047$. As depicted in Figure 2, those in the active tDCS condition reported significantly higher levels of state anxiety post worry-induction compared to those in the sham condition, $t(91)=2.45$, $p=.016$, $d=0.51$, but state anxiety did not significantly differ between groups at any other time point (all $t<1.11$, all $p<.268$).

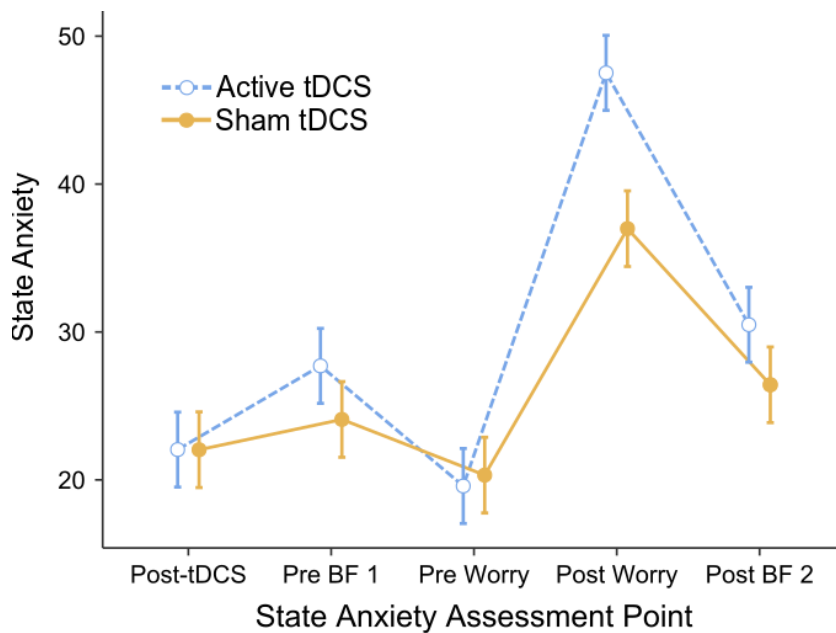


Figure 2. Levels of state anxiety at each assessment point across active and sham tDCS groups. Error bars show standard error of the mean.

To assess the degree to which this effect was driven by the relative increase in state anxiety in response to the worry induction, or the subsequent decrease in state anxiety response to the breathing focus task, a follow-up analysis was conducted on the magnitude of change in state anxiety before and after worry induction. Worry Induction Reactivity

scores were computed subtracting post-worry STAI-S from pre-worry STAI-S. Worry Induction Recovery scores were similarly computed by subtracting post breathing-focus 2 STAI-S from post-worry STAI-S. Positive values for these scores represent greater anxiety reactivity (increase in state anxiety), and negative values represent greater anxiety recovery (decrease in state anxiety).

As depicted in Figure 3, a two-way tDCS condition \times anxiety change assessment period ANOVA showed a significant interaction, $F(1, 91)=7.52$, $p=.007$, $\eta_p^2=0.076$, whereby the effect on anxiety was carried both by greater anxiety reactivity in the active tDCS group in response to the worry induction, $t(91)=2.93$, $p=.004$, $d=0.72$, and also greater anxiety recovery in the tDCS group compared to the sham group $t(91)=2.05$, $p=.043$, $d=0.43$.

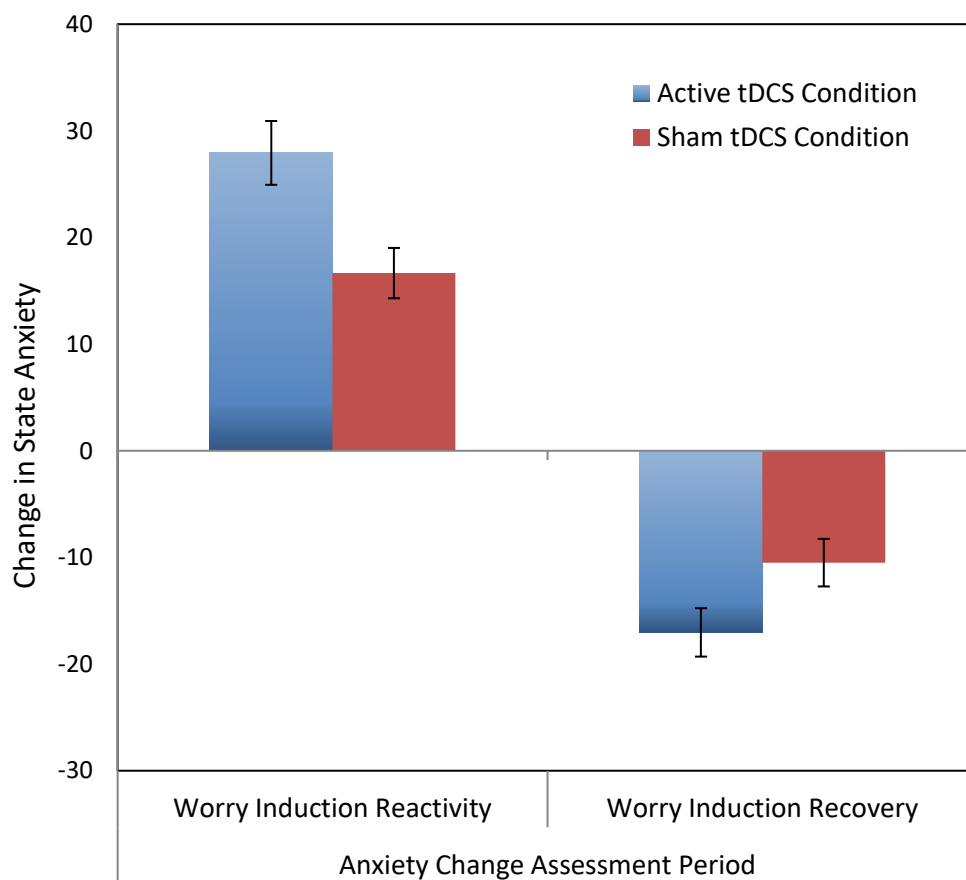


Figure 3. Change in state anxiety from pre to post worry induction (Worry reactivity) and from post worry-induction to post breathing focus 2 (Worry recovery).

Discussion

The present study aimed to assess the impact of tDCS on worry in terms of its immediate effects on negative intrusive thoughts and worry-related emotional reactivity. Secondly, we sought to examine whether concurrent engagement in a mindful task during tDCS delivery would further augment any observed effects. Regarding the first aim, the active tDCS group showed significantly larger elevations in state anxiety in response to instructed worry as compared to the sham stimulation group. Moreover, the active tDCS group also showed greater subsequent anxiety recovery compared to the sham stimulation group. The greater effect of anxiety recovery observed for the active tDCS group must be interpreted with caution however, as the larger increase in anxiety for this group could also contribute to the larger subsequent reduction via regression to the mean. Nevertheless, this pattern of effects is entirely consistent with the hypothesis that left DLPFC tDCS enhances goal-oriented cognition, whereby intentional engagement in worry contributed to larger increases in anxiety, while subsequent non-worry engagement during the breathing focus task contributed to larger decreases in anxiety. No effects of tDCS on negative intrusive cognitions were observed.

The observed interactive effect between tDCS and worry induction on anxiety are entirely consistent with recent findings showing that left frontal tDCS can increase or decrease emotional reactivity to negative content according to an individual's current intent (Marques et al., 2018). Given findings showing that left DLPFC stimulation can attenuate negative cognition (De Raedt et al., 2017), and reduce reactivity to negative content (Peña-Gómez et al., 2011) it seems highly unlikely that the present results reflect any general

anxiogenic effects of this stimulation. It appears more likely that increased left DLPFC activity contributes to the enhancement of goal-directed cognition which can be deployed in line with an individual's active intent. In this instance, the active intent consisted of motivated engagement in worry and a consequent increase in anxiety, but also a greater subsequent reduction in worry when the individual's cognitive goals shifted to a non-worry focus. Thus, the current findings are consistent with the position that the emotional effects of tDCS may depend in part on an individual's current cognitive goals, with motivated engagement in worry potentially contributing to heightened anxiety.

While the current study is the first to examine the effects of tDCS on intentional worry, it is relevant to consider these findings in relation to research examining the effects of tDCS on similar cognitive processes in the form of rumination. De Raedt et al. (2017) found that left DLPFC tDCS contributed to a spontaneous reduction in self-reported ruminative self-referential thoughts, a decrease which persisted following exposure to a criticism challenge. Kelley et al. (2013) also found that following an anger-induction procedure, there was an increase in the frequency of ruminative thoughts for those receiving right DLPFC tDCS (relative to both left and sham) but no significant increase in rumination for left DLPFC stimulation. In both of these studies the rumination examined was spontaneous, and not instructed. Given these findings, future research could usefully examine whether left DLPFC tDCS would increase the cognitive and/or emotional effects of intentional rumination in line with the current findings, and conversely, whether the presence of a worry-inducing stressor in the absence of instructed worry, would contribute to reductions, rather than increases in anxiety and worry.

In relation to the second aim of the study, we found no evidence that engagement in a mindful task during the completion of tDCS had an effect on intrusive cognitions or anxiety,

and no evidence that it augmented the effects of tDCS on these processes. This pattern of effects is generally inconsistent with prior studies that have shown larger effects of combined stimulation with cognitive training (Martin et al., 2013). However, it is important to consider a number of factors that could have contributed to the absence of effects on negative intrusions and of the mindfulness condition.

One factor which may have limited the impact of the mindfulness and/or tDCS manipulation is the generally low levels of anxiety in the sample, as reflected by average DASS anxiety scores falling well within the 'normal' range (Lovibond & Lovibond, 1995). These levels of anxiety are also consistent with the low rates of intrusive thoughts observed in comparison to studies with high anxious/worry samples (e.g. Hayes, Hirsch, & Mathews, 2010). Thus while the sample may have been well suited to capturing relative increases in anxiety from this low baseline, rates of negative thought intrusions may have been close to 'floor' in this sample, meaning that further tDCS or mindfulness-induced reductions were unlikely. Future research could therefore employ a similar design among a sample with elevated levels of anxiety to assess whether tDCS in isolation, or combined with mindfulness contributes to reductions in negative intrusive thoughts for those who are likely to experience a higher baseline frequency of such cognitions.

In considering potential reasons for the absence of effects on thought intrusions, it is possible that the mindfulness conditions in the current study could potentially have obscured main effects of tDCS that might otherwise have emerged. While no effects of mindfulness condition were recorded, these two conditions could potentially have added noise to the data. For example, if tDCS enhanced individual differences in the tendency to focus on negative or positive content while engaged in mindfulness or (particularly) mind wandering, such increased variance could in principle have obscured tDCS-induced

differences in intrusive thoughts. Future research might therefore be well served by replicating the current design in the absence of the alternative mindfulness conditions.

It should also be acknowledged that while the present study targeted the left DLPFC, there is considerable potential for current spread when using tDCS (Keeser et al., 2011; Stagg et al., 2013) which could therefore implicate nearby regions. For example, research suggesting that the DLPFC has few direct anatomic projections to the amygdala (Barbas, 2000) has led some models to suggest that the DLPFC may exert effects on emotion via the VLPFC (Hartley & Phelps, 2010; Ochsner et al., 2012). Indeed, Marques et al. (2018) found that stimulation of the VLPFC but not the DLPFC contributed to enhancement of emotional regulation. As such, while the results of the current study are consistent with the role of the DLPFC in the enhancement of goal-directed emotional cognition, it does not preclude the possibility that this effect may be due to spreading activation to adjacent regions.

An additional limitation of the current study was experimenter awareness of tDCS condition. While computerised delivery of the thought intrusion and anxiety assessment measures minimised the likelihood of demand effects, the fact that the study was not double blind means that it is not possible to rule out such effects. As such future studies would ideally permit double blinding to exclude this possibility.

While the use of a healthy sample means that extreme caution is warranted in considering any potential clinical relevance, the current results may hold general implications for the application of tDCS in emotional pathology. Most directly, these findings highlight the possibility that motivated engagement in worry in close proximity to the delivery of tDCS could conceivably contribute to elevations in anxiety. This may be relevant for disorders where motivated engagement in repetitive negative thinking is known to be a feature (e.g. GAD, depression; Ehring & Watkins, 2008), where individuals may experience

increases in emotional reactivity when such processes are engaged in close proximity to neurostimulation. A further implication is that complimenting neurostimulation with cognitive training that discourages patterns of negative cognition could conceivably enhance emotional benefits. The validity of such clinical implications will obviously depend on the replication and extension of the current findings with high/clinically anxious samples.

While future extensions with high and/or clinically anxious samples will be informative, experimental work focused on healthy samples can be critical prior to application with more highly anxious groups. This is particularly the case for neurostimulation research where effects of active stimulation can occasional produce outcomes that may be detrimental (e.g. Abend et al., 2016). As with the current findings, where active tDCS was shown to potentiate anxiety reactivity to instructed worry, the potential for neurostimulation to produce anxiogenic effects under specific conditions underscores the importance of preliminary experimental work with non/sub-clinical populations prior to application with emotionally vulnerable populations.

References

- Abend, R., Jalon, I., Gurevitch, G., Sar-el, R., Shechner, T., Pine, D. S., . . . Bar-Haim, Y. (2016). Modulation of fear extinction processes using transcranial electrical stimulation. *Translational Psychiatry*, 6, e913. doi:10.1038/tp.2016.197
- Andrews, S. C., Hoy, K. E., Enticott, P. G., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. *Brain stimulation*, 4(2), 84-89.
- Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain research bulletin*, 52(5), 319-330.
- Baumert, A., Buchholz, N., Zinkernagel, A., Clarke, P., MacLeod, C., Osinsky, R., & Schmitt, M. (2019). Causal underpinnings of working memory and Stroop interference control: Testing the effects of anodal and cathodal tDCS over the left DLPFC. *Cognitive, Affective, & Behavioral Neuroscience*. doi:10.3758/s13415-019-00726-y
- Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: an integrative account. *Trends in Cognitive Sciences*, 11(7), 307-316. doi:10.1016/j.tics.2007.05.008
- Borkovec, T. D., Hazlett-Stevens, H., & Diaz, M. L. (1999). The role of positive beliefs about worry in generalized anxiety disorder and its treatment. *Clinical Psychology & Psychotherapy*, 6(2), 126-138. doi:10.1002/(sici)1099-0879(199905)6:2<126::Aid-cpp193>3.0.Co;2-m
- Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., . . . Alonzo, A. (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *The British Journal of Psychiatry*, 208(6), 522-531.

- Chen, N. T. M., Basanovic, J., Notebaert, L., MacLeod, C., & Clarke, P. J. F. (2017). Attentional bias mediates the effect of neurostimulation on emotional vulnerability. *Journal of Psychiatric Research*, 93, 12-19. doi:10.1016/j.jpsychires.2017.05.008
- Chiesa, A., Serretti, A., & Jakobsen, J. C. (2013). Mindfulness: Top–down or bottom–up emotion regulation strategy? *Clinical Psychology Review*, 33(1), 82-96.
doi:<https://doi.org/10.1016/j.cpr.2012.10.006>
- Clarke, P. J. F., Browning, M., Hammond, G., Notebaert, L., & MacLeod, C. (2014). The Causal Role of the Dorsolateral Prefrontal Cortex in the Modification of Attentional Bias: Evidence from Transcranial Direct Current Stimulation. *Biological Psychiatry*, 76(12), 946–952. doi:10.1016/j.biopsych.2014.03.003
- De Raedt, R., Remue, J., Loeys, T., Hooley, J. M., & Baeken, C. (2017). The effect of transcranial direct current stimulation of the prefrontal cortex on implicit self-esteem is mediated by rumination after criticism. *Behaviour Research and Therapy*, 99, 138-146. doi:<https://doi.org/10.1016/j.brat.2017.10.009>
- Ehring, T., & Watkins, E. R. (2008). Repetitive Negative Thinking as a Transdiagnostic Process. *International Journal of Cognitive Therapy*, 1(3), 192-205.
doi:10.1521/ijct.2008.1.3.192
- Hartley, C. A., & Phelps, E. A. (2010). Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology*, 35(1), 136-146.
- Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage*, 59(1), 750-760.
doi:10.1016/j.neuroimage.2011.07.008

- Hayes, S., Hirsch, C. R., Krebs, G., & Mathews, A. (2010). The effects of modifying interpretation bias on worry in generalized anxiety disorder. *Behaviour Research and Therapy*, 48(3), 171-178. doi:10.1016/j.brat.2009.10.006
- Hayes, S., Hirsch, C. R., & Mathews, A. (2010). Facilitating a benign attentional bias reduces negative thought intrusions. *Journal of Abnormal Psychology*, 119(1), 235-240.
- Heeren, A., Billieux, J., Philippot, P., De Raedt, R., Baeken, C., de Timary, P., . . . Vanderhasselt, M.-A. (2017). Impact of transcranial direct current stimulation on attentional bias for threat: a proof-of-concept study among individuals with social anxiety disorder. *Social Cognitive and Affective Neuroscience*, 12(2), 251-260. doi:10.1093/scan/nsw119
- Hirsch, C. R., MacLeod, C., Mathews, A., Sandher, O., Siyani, A., & Hayes, S. (2011). The contribution of attentional bias to worry: Distinguishing the roles of selective engagement and disengagement. *Journal of Anxiety Disorders*, 25(2), 272-277. doi:10.1016/j.janxdis.2010.09.013
- Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology*, 78(2), 169-183. doi:10.1037/a0018555
- Inquisit 4.0.8. (2015). *Millisecond Software LLC [Computer software]*: Seattle, WA.
- Ironside, M., Browning, M., Ansari, T. L., Harvey, C. J., Sekyi-Djan, M. N., Bishop, S. J., . . . O'Shea, J. (2019). Effect of Prefrontal Cortex Stimulation on Regulation of Amygdala Response to Threat in Individuals With Trait Anxiety: A Randomized Clinical Trial. *Jama Psychiatry*, 76(1), 71-78. doi:10.1001/jamapsychiatry.2018.2172 %J JAMA Psychiatry

- Ironside, M., O'Shea, J., Cowen, P. J., & Harmer, C. J. (2016). Frontal Cortex Stimulation Reduces Vigilance to Threat: Implications for the Treatment of Depression and Anxiety. *Biological Psychiatry*, 79(10), 823-830. doi:10.1016/j.biopsych.2015.06.012
- Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., . . . Padberg, F. (2011). Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. *31*(43), 15284-15293. doi:10.1523/JNEUROSCI.0542-11.2011 %J The Journal of Neuroscience
- Kelley, N. J., Hortensius, R., & Harmon-Jones, E. (2013). When Anger Leads to Rumination: Induction of Relative Right Frontal Cortical Activity With Transcranial Direct Current Stimulation Increases Anger-Related Rumination. *24*(4), 475-481. doi:10.1177/0956797612457384
- Lovibond, P., & Lovibond, S. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, 33(3), 335-343.
- Marchand, W. R. (2014). Neural mechanisms of mindfulness and meditation: Evidence from neuroimaging studies. *World journal of radiology*, 6(7), 471-479. doi:10.4329/wjr.v6.i7.471
- Marques, L. M., Morello, L. Y. N., & Boggio, P. S. (2018). Ventrolateral but not Dorsolateral Prefrontal Cortex tDCS effectively impact emotion reappraisal – effects on Emotional Experience and Interbeat Interval. *Scientific Reports*, 8(1), 15295. doi:10.1038/s41598-018-33711-5
- Marteau, T. M., & Bekker, H. (1992). The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *British Journal of Clinical Psychology*, 31(3), 301-306. doi:10.1111/j.2044-8260.1992.tb00997.x

- Martin, D. M., Liu, R., Alonzo, A., Green, M., Player, M. J., Sachdev, P., & Loo, C. K. (2013). Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *International Journal of Neuropsychopharmacology*, 16(9), 1927-1936. doi:10.1017/s1461145713000539
- Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, 1251(1), E1-E24.
- Peña-Gómez, C., Vidal-Piñero, D., Clemente, I. C., Pascual-Leone, Á., & Bartrés-Faz, D. (2011). Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. *PLoS ONE*, 6(7), e22812.
- Ruscio, A. M., & Borkovec, T. D. (2004). Experience and appraisal of worry among high worriers with and without generalized anxiety disorder. *Behaviour Research and Therapy*, 42(12), 1469-1482. doi:10.1016/j.brat.2003.10.007
- Sagliano, L., Atripaldi, D., De Vita, D., D'Olimpio, F., & Trojano, L. (2019). Non-invasive brain stimulation in generalized anxiety disorder: A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 93, 31-38. doi:10.1016/j.pnpbp.2019.03.002
- Sanchez-Lopez, A., Vanderhasselt, M.-A., Allaert, J., Baeken, C., De Raedt, R. J. C., Affective, & Neuroscience, B. (2018). Neurocognitive mechanisms behind emotional attention: Inverse effects of anodal tDCS over the left and right DLPFC on gaze disengagement from emotional faces. 18(3), 485-494. doi:10.3758/s13415-018-0582-8
- Stagg, C. J., Lin, R. L., Mezue, M., Segerdahl, A., Kong, Y., Xie, J., & Tracey, I. (2013). Widespread Modulation of Cerebral Perfusion Induced during and after Transcranial

Direct Current Stimulation Applied to the Left Dorsolateral Prefrontal Cortex. 33(28), 11425-11431. doi:10.1523/JNEUROSCI.3887-12.2013 %J The Journal of Neuroscience

Vicario, C. M., Salehinejad, M. A., Felmingham, K., Martino, G., & Nitsche, M. A. (2019). A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience & Biobehavioral Reviews*, 96, 219-231. doi:10.1016/j.neubiorev.2018.12.012